TUMOR CELL-DERIVED EXOSOMES AND METHOD OF TREATING COLORECTAL CANCER

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 62/962,312 filed on Jan. 17, 2020, the contents of which are incorporated by reference in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

[0002] N/A

BACKGROUND OF THE INVENTION

[0003] Colorectal cancer (CRC) remains the third most common cause of cancer-related deaths in the United States. Approximately 85% of CRC tumors are nonimmunogenic (i.e. they lack a significant number of tumor-infiltrating T cells) and are typically unresponsive to current immune checkpoint inhibitor-based therapies. Tumor-derived exosomes (or extracellular vesicles (EVs)) have been identified as a major source of tumor antigens that can stimulate tumor-specific immunity. However, immunosuppressive factors, such as PD-L1 and miRNAs that target T-cell activation, were also identified in the tumor-derived EVs. It has been shown that these immunosuppressive components compromise the tumor immunity stimulating effects of tumor-derived EVs, leading to immunosuppression in the cancer patients.

[0004] Thus, there is a need in the art for compositions and methods for increasing the immune response to tumors and for increasing the efficacy of checkpoint blockades for cancer treatment.

SEQUENCE LISTING

[0005] A Sequence Listing accompanies this application and is submitted as an ASCII text file of the sequence listing named "920171_00394_ST25.txt" which is 5.94 KB in size and was created on Jan. 14, 2021. The sequence listing is electronically submitted via EFS-Web with the application and is incorporated herein by reference in its entirety.

SUMMARY OF THE INVENTION

[0006] In some aspects, the present disclosure provides modified tumor-derived extracellular vesicles (EVs) isolated from a tumor cell having reduced or lacking expression of an immune suppressive factor. In a preferred embodiment, the immune suppressive factor is miR-424. These modified tumor-derived EVs may be used as a vaccine for treating tumors by increasing the immune response to the tumors, more particularly secondary tumors which which are distal to the primary tumor site.

[0007] In another aspect, the present disclosure provides a composition comprising one or more tumor-derived EVs and a pharmaceutically acceptable carrier. In some aspects, the two or more EVs are from the same tumor type.

[0008] In another aspect, the present disclosure provides a method of producing a tumor-derived extracellular vesicle (EV) substantially lacking expression of an immune suppressive factor, preferably miR-424, the method comprising (a) providing a modified tumor cell that lacks expression of the immune suppressive factor and can produce EVs; and (b) isolating EVs produced by the tumor cell, wherein the EVs substantially lack expression of the immune suppressive factor, preferably miR-424.

[0009] In another aspect, the present disclosure provides a method of treating cancer in a subject comprising administering an effective amount of tumor-derived EVs to a subject in need thereof. The EVs should substantially lack expression of an immune suppressive factor or miR-424 and should comprise one or more cancer antigen.

[0010] In yet another aspect, the present disclosure provides a method of stimulating an anti-tumor response in a subject having cancer. The method involves administering a vaccine comprising tumor-derived EVs described herein or the composition described herein to a subject having cancer in an amount effective to elicit an anti-tumor response in the subject.

[0011] In another aspect, the present disclosure provides a method of sensitizing a tumor cell in a subject to immune checkpoint inhibitors. The method involves administering one or more tumor-derived EVs described herein or the composition described herein to a subject having cancer and subsequently administering one or more checkpoint inhibitors to the subject. In some aspects, the checkpoint inhibitor is a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA-4 inhibitor or combinations thereof.

[0012] In another aspect, the present disclosure provides a method of preventing, reducing or inhibiting tumor cell growth in a subject. The method involves administering an effective amount of a vaccine comprising tumor-derived EVs to a subject in need thereof to prevent, reduce, or inhibit tumor cell growth. The EVs should substantially lack expression of an immune suppressive factor or miR-424. In some aspects, the cancer to be inhibited is adenocarcinoma from an adenoma.

[0013] In another aspect, the present disclosure provides a method of preventing the growth of a secondary tumor in a subject following resection of a primary tumor. The method involves administering an effective amount of a vaccine comprising tumor-derived EVs to the subject. The EVs should substantially lack expression of an immune suppressive factor or miR-424.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0015] FIGS. **1**A-**1**D. In FIG. **1**A, T-cell infiltration (CD3) was evaluated in human colorectal cancer (CRC) patients' samples using immunofluorescent staining. The bar graph below depicts the total number of cases of microsatellite stable (MSS) subtype CRC tumors and microsatellite instability (MSI) subtype CRC tumors that exhibited high T-cell infiltration and low T-cell infiltration in this assay. In FIG. **1**B, expression of CD28 was measured on $CD4^+$ T-cells and $CD8^+$ T-cells, and expression of CD80 and CD86 was measured on DCs by performing flow cytometry on CRC colon tissues and paired normal colon tissues. In FIG. **1**C, the results of FIG. **1**B were confirmed by performing immunofluorescent staining. Assayed markers include: CD28 expression on CRC tumor infiltrating T-cells (left), CD80